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No effect of a homoeopathic combination of *Arnica montana* and *Bryonia alba* on bleeding, inflammation, and ischaemia after aortic valve surgery

Catherine Cornu,[1] Pierre Joseph,[2] Ségolène Gaillard,[1] Christian Bauer,[2] Catherine Vedrinne,[2] Alvine Bissery,[3] Ghislaine Melot,[1] Nadine Bossard,[3] Philippe Belon[4] & Jean-Jacques Lehot[2]

[1]INSERM, CIC 201, Lyon, Hospices Civils de Lyon, Service de Pharmacologie Clinique, Lyon, Université de Lyon, Lyon and CNRS, UMR 5558, Lyon, [2]Hospices Civils de Lyon, Hôpital Louis Pradel, Service d'Anesthésie-Réanimation, Bron, Université Lyon I, Villeurbanne, INSERM, ERI 22, Lyon, [3]Hospices Civils de Lyon, Service de Biostatistique, Lyon, Université de Lyon, Lyon, Université Lyon I, Villeurbanne, CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique Santé, Pierre-Bénite, and [4]Formerly, Laboratoires Boiron, St Foy-lès-Lyon, France

Correspondence
Dr Catherine Cornu, INSERM CIC 201, Hôpital Cardiovasculaire et Pneumologique, 28, Avenue du Doyen Lépine, F-69677 Bron Cedex, France.
Tel: + 33 4 7235 7231
Fax: + 33 4 7235 7364
E-mail: catherine.cornu@chu-lyon.fr

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Arnica and other homoeopathic extracts have been used in various obstetrical, surgical and postsurgical conditions in attempts to control inflammation, swelling and haemorrhage with controversial results.
- However, no homoeopathic combination with haemostatic and anti-inflammatory properties has been used in cardiac surgery that is often followed by haemorrhage and involves substantial systemic inflammation.
- In this setting, exudation and blood loss are precisely quantified.

WHAT THIS STUDY ADDS

- A homoeopathic combination of *Arnica montana* and *Bryonia alba* was used in aortic valve surgery in a prospective double-blind, randomized, placebo-controlled clinical trial to evaluate its effectiveness.
- This combination did not show any benefit in avoiding bleeding, pain, inflammation, and myocardial ischaemia.

AIMS

Arnica montana is a popular homoeopathic treatment with potential haemostatic and anti-inflammatory properties. A homoeopathic combination of *A. montana* and *Bryonia alba* was used in aortic valve surgery to evaluate its effectiveness in reducing bleeding, inflammation, pain and myocardial ischaemia.

METHODS

One day before surgery, 92 adult patients were randomly assigned to a double-blind parallel trial with either homoeopathic granules or a matching placebo until 4 days after surgery. The primary outcome was the volume of blood/liquid in the drains at their removal. The secondary outcomes included postoperative blood/liquid losses at 12 and 24 h as well as C-reactive protein (CRP), pain, temperature and plasma troponin Ic.

RESULTS

At 12 h and 24 h after surgery, then at drain removal, blood losses in homoeopathy and placebo groups were not statistically significant (362 ± 218, 520 ± 269 and 640 ± 297 ml *vs.* 456 ± 440, 620 ± 477 and 796 ± 717 ml; $P = 0.19$, 0.23 and 0.35, respectively). The statistical modelling did not show significantly different patterns of CRP, troponin and body temperature changes or of pain perception. The number of transfused packed red cells was not significantly different either ($P = 0.58$). Two patients from each group died during the study period and the number of serious adverse events was not statistically different (six in homoeopathy *vs.* 10 in placebo groups; Fisher's exact test $P = 0.41$).

CONCLUSIONS

In the study setting, there was no evidence of effects of *A. montana* and *B. alba* combination on bleeding, inflammation, pain or myocardial ischaemia.

Introduction

Homoeopathic treatments are widely prescribed worldwide. Today, in both Europe and the USA, *Arnica* is a popular homoeopathic treatment for acne, bruises, sprains, muscle aches and a general topical counterirritant. Oral *Arnica* has been also used for the relief of mouth and throat inflammation and for the treatment of postsurgical bruising and swelling [1]. *Arnica* and other homoeopathic extracts have even been used in various surgical and obstetrical conditions with controversial effects [2–9]. Because cardiac surgery is often followed by haemorrhage and involves substantial systemic inflammation, it provided an opportunity to test conventional or homoeopathic drugs with haemostatic and anti-inflammatory properties [10–12].

Bryonia alba is a curcurbitacea whose roots contain highly oxygenated and unsaturated bitter compounds such as the tetracyclic triterpenoid called cucurbitacine D. These compounds possess cytotoxic and antitumour properties [13]. Their administration in humans induces dryness of the respiratory and digestive mucous membranes expressed by thirst. The clinical use of *B. alba* is recommended for acute serositis, i.e. meningitis, pericarditis, peritonitis or arthritis [14–16]. It has been used in inflammation following surgery [7], without proven efficacy, and postpartum to inhibit unwanted lactation [17].

In the present study, *A. montana* and *B. alba* were administered perioperatively in a placebo-controlled, double-blind clinical trial to patients undergoing aortic valve replacement to evaluate: (i) inflammation; through pain, C-reactive protein (CRP), body temperature, healing of sternotomy; and (ii) bleeding; through drainage volume, transfusion of labile blood products, and haematocrit. Moreover, because inflammation and myocardial injury have been correlated in cardiac surgery, plasma troponin Ic was also studied.

Materials and methods

Design

Between November 2004 and June 2007, 92 patients were enrolled in a prospective double-blind, randomized, placebo-controlled clinical trial carried out in a single university hospital department.

The study protocol was approved by the Ethics Committee of Lyon Sud-Est 2 on 25 August 2004. The prospective patients were informed of the study as soon as they received an appointment for surgery. During the preoperative visit on the day before surgery, they were given oral and written information and were included if they gave written informed consent. The active drugs and placebo were assigned using a permuted-block algorithm. Concealed allocation was centralized by a phone call to the coordination centre after eligibility check and baseline data collection.

Patients were male and female, >18 years old, for whom an elective aortic valve surgery was planned. Exclusion criteria included inflammatory or infectious evolving diseases, allergy to one of the study treatments, use of chronic nonsteroidal or steroidal anti-inflammatory drugs within 3 days before surgery, cardiac surgery involving other parts of the heart than the aortic valve, and iterative cardiac surgery.

All cardiac medications were continued until the day of surgery. Oral hydroxyzine 100 mg and alprazolam 0.5 mg were given 1 h prior to anaesthesia, and induction of anaesthesia consisted of sufentanil 5 $\mu g\ kg^{-1}$ and midazolam 5 mg. Cisatracurium besilate (0.15 $mg\ kg^{-1}$) was administered to facilitate laryngoscopy and orotracheal intubation. Anaesthesia was maintained by total intravenous (i.v.) administration of propofol and increments of sufentanil. Mechanical ventilation was provided by a Julian ventilator (Dragër, Lubeck, Germany) with an oxygen–nitrogen 50/50 mixture. Prior to cardiopulmonary bypass (CPB), unfractionated heparin (300 IU kg^{-1}) was administered intravenously. A membrane oxygenator (Affinity®; Medtronic, Minneapolis, MN, USA) and a nonpulsatile pump (SS®; Stockert, Sorin Group, München, Germany) were used. Bladder temperature was kept between 35 and 37°C during CPB. The CPB priming consisted of Ringer's lactated solution (1000 ml) and unfractionated heparin (5000 IU). Saint Thomas's Hospital crystalloid cardioplegic solution (12 ml kg^{-1}) was injected at 4°C into the aortic root immediately after aortic cross-clamping and then every 20 min during cross-clamping. The perfusion index was maintained at 2.4 l min^{-1}, and the mean arterial pressure between 50 and 80 mmHg by vasopressors and by adjusting propofol infusion rate. At the end of CPB, the oxygenator content was transfused into the patient. Reversal of heparin was accomplished with protamine sulphate (400 IU kg^{-1}). Tranexamic acid 15 $mg\ kg^{-1}$ was administered intravenously immediately before and after CPB. At chest closure, two mediastinal drains were inserted. In the postoperative intensive care unit, propofol was administered during 1–4 h up to tracheal extubation. Analgesia was administered to all patients by i.v. paracetamol 1 g every 6 h and nefopam 100 mg per 24 h when not contraindicated. Moreover, morphine chlorhydrate was provided by patient-controlled analgesia (PCA, APM®; Abbott, Abbott Park, IL, USA) programmed with a bolus of 1 mg, a refractory period of 10 min and a maximal dose of 20 mg every 4 h during 4 days. Most patients went to the step-down unit on the first postoperative day. The two mediastinal drains were removed when the drainage volume dropped to <100 ml per 24 h, usually on the second postoperative day.

Objectives and end-points

The primary end-point was blood loss after surgery until drain removal. The secondary end-points included: plasma CRP variation (immunoturbidimetry, Architect®; Abbott)

from inclusion until day 2 and day 7 after surgery; body temperature b.i.d. during days 1 and 2 after surgery; packed red cell transfusion (when haemoglobin concentration was <70 g l^{-1} during surgery and 80 g l^{-1} after surgery) during hospital stay; self-evaluation of pain using a visual analogue scale (VAS); troponin Ic plasma concentration variations (immuno-enzymo chemiluminescence, Architect®; Abbott) from inclusion to days 1 and 2 after surgery; and duration between the end of CPB and thorax closure.

Sample size

In this pilot study, for feasibility reasons, we planned to include 90 subjects, 45 per group. This sample size would allow to detect a 25% reduction of blood loss with a 90% power ($\alpha = 0.05$) considering a baseline value of 800 ml (SD 300 ml) in the placebo group. This value was extrapolated from a meta-analysis by Levi *et al*. in which the reduction in blood losses varied between 49.5 ml (aprotinin *vs.* lysine analogues) and 446.5 ml (aprotinin *vs.* placebo) [11].

Homoeopathic treatment

The study drug was an association of *A. montana* 5 CH and *B. alba* 5 CH (Centesimal Hahnemanian scale; i.e. a 1 : 100 dilution). Five granules of each drug or matching placebos were given during five consecutive days, twice a day, starting on the evening before surgery. This treatment was added to other analgesic treatments. The studied drugs and the placebos were manufactured, packaged and supplied by Laboratoires Boiron (Sainte-Foy-lès-Lyon, France).

Statistical analysis

The analyses were performed according to the intention to treat principle: patients were kept in their initial randomization group regardless of subsequent protocol deviations. Quantitative variables were compared using Student's *t*-tests for normal distributions and Mann–Whitney tests for skewed distributions. Comparisons of qualitative variables were made using Fisher's exact test.

Linear mixed regressions (with fixed and random effects) were used to model the evolution of CRP and troponin along time. These variables were used as dependent variables. Random effects on the intercept and on the slope of the regression line were used to take into account and quantify heterogeneity between subjects. The treatment group was introduced in the model as a fixed-effect covariate. An interaction term between 'group' and 'time since inclusion' was introduced in the model to compare group evolutions.

Regarding the main outcome, comparisons with *P*-values ≤ 0.05 were considered significant. The statistical analyses were carried out with STATA 10.0 software (Stata Corp, College Station, TX, USA). Statistical analyses and generation of the sequence of allocation were performed by the same statistical team.

Results

The flow diagram of patient inclusion is shown in Figure 1. The baseline characteristics of participant patients are shown in Table 1. At baseline, patient distribution between the homoeopathy and placebo groups was homogeneous and their characteristics comparable.

Blood losses

At drain removal, the 157-ml difference in the mean volumes of blood losses between the homoeopathy and placebo groups was not statistically significant ($P = 0.35$). The use of a nonparametric approach, namely a bootstrap method, led to a (–48, 445) 95% confidence interval (CI). The mean blood losses at 12 h and 24 h after surgery were also nonsignificantly different ($P = 0.19$ and 0.23, respectively) (Table 2).

Other end-points

The mean values of CRP at baseline and at day 2 and day 7 after surgery are shown in Table 2. From the mixed linear regression models, the slopes from baseline to day 2 (all positive) and from day 2 to day 7 (all negative) did not significantly differ between the two groups (Figure 2a). The changes in body temperature and pain (VAS) from end of surgery to day 7 did not differ either (Figure 2b,c). Precisely, the mean VAS did not differ significantly between the two groups at 6, 12, 24, 36, 48, 54, 60, 96 and 168 h, and the number of patients with VAS over 40 mm did not differ either. Until day 2 after surgery, the changes in blood troponin Ic were not significantly different between the two groups; the values at 6, 24 and 48 h did not differ significantly ($P = 0.98$, 0.19 and 0.13, respectively). From the mixed linear regression models, the slopes from baseline to 6 h (all positive) and from 6 h to 48 h (all negative) did not differ significantly between the two groups (Figure 2d). Fifteen patients (33%) in the homoeopathy group and 12 (26%) in the placebo group received packed red-cell transfusion ($P = 0.58$).

Two patients from each group died during the study period. The causes of death were: septic shock, severe cardiac and kidney failures, sudden death, and cerebral haemorrhage.

One patient in the homoeopathy group and three in the placebo group had major cardiovascular events (pericardial effusion/severe bleeding requiring iterative surgery). Three patients of the homoeopathy group and six in the placebo group had other severe nonfatal cardiovascular events (arrhythmia, haemorrhage/pericardial effusion, embolic stroke). One participant in the placebo group had a severe nonfatal noncardiovascular event: a mood disorder and delirium. Six patients (13.04%) in the homoeopathy group *vs.* 10 (21.74%) in the placebo group had a serious adverse event, including death; ($P = 0.41$, Fisher's exact test).

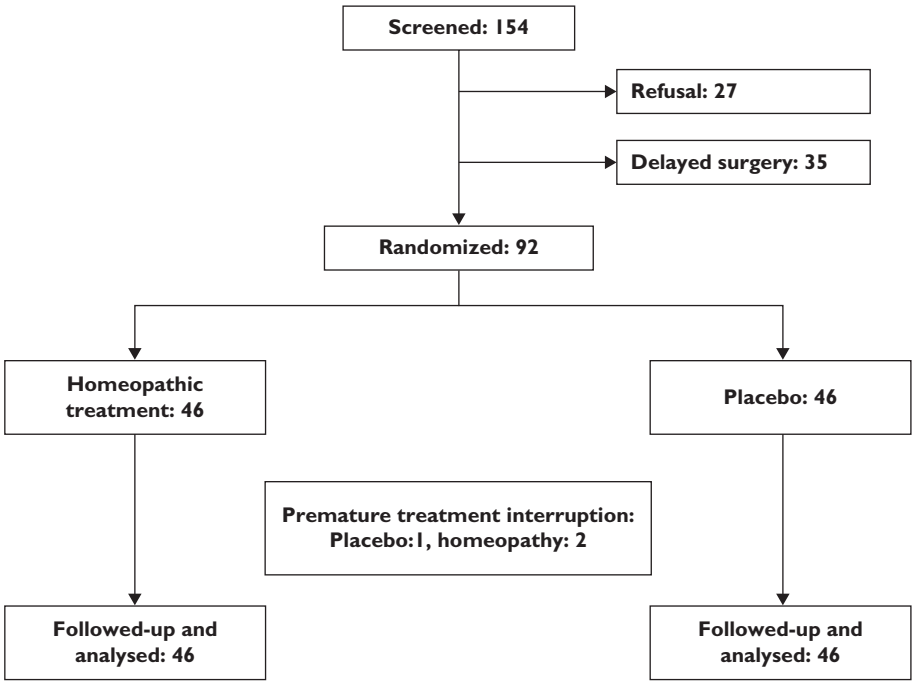

Figure 1
Flow diagram of patients

Table 1
Baseline characteristics of patients

Characteristics	Homoeopathy (n = 46)	Placebo (n = 46)	P-value
Males	25 (54)	29 (63)	0.53
Age (years)	72 ± 8	70 ± 11	
Body mass index (kg m^{-2})	27.5 ± 5.8	26.3 ± 3.8	
Systolic blood pressure (mmHg)	131 ± 19	130 ± 19	
Diastolic blood pressure (mmHg)	69 ± 11	70 ± 10	
C-reactive protein (mg l^{-1})	5.96 ± 7.96	4.19 ± 6.99	0.27
Troponin I at inclusion (μg l^{-1})	0.04 ± 0.08	0.04 ± 0.04	
Type of aortic valve disorder			0.97
Aortic stenosis	30 (65)	31 (67)	
Aortic insufficiency	3 (7)	3 (7)	
Mixed valvulopathy	13 (28)	12 (26)	
Associated cardiovascular diseases	44 (95.6)	42 (91.3)	0.68
Left ventricular hypertrophy	26 (59)	30 (71)	0.26
Ischaemic heart disease	4 (9)	0	0.12
Mitral valve disorder	4 (9)	2 (5)	0.68
Other	36 (81.8)	34 (81)	1
Anticoagulants drugs at inclusion	23 (50)	17 (37)	0.29

Values are either n (%) with P-value by Fisher's exact test or mean ± SD with P-value by Student's t-test.

Table 2
Major end-points

End-points	Homoeopathy (n = 46)	Placebo (n = 46)	P-value
Primary end-point			
Cumulated blood loss at drain removal (ml)	640 ± 297	796 ± 717	0.35
Secondary end-points			
Blood loss at 12 h (ml)	362 ± 218	456 ± 440	0.19
Blood loss at 24 h (ml)	520 ± 269	620 ± 477	0.23
C-reactive protein (mg l^{-1})			
At day 2	263.7 ± 81.9	250.3 ± 82.1	0.23
At day 7	75.4 ± 54.8	76.3 ± 43.3	0.54
Troponin I (μg l^{-1})			
Six hours after surgery	3.49 ± 5.86	2.72 ± 1.47	0.99
24 h after surgery	3.69 ± 8.61	1.93 ± 1.41	0.19
48 h after surgery	2.03 ± 3.71	1.11 ± 0.95	0.13
New atrial fibrillation on day 1 or 2	7 (15)	3 (6)	0.36
Cumulated morphine (mg)	45.0 ± 27.7	37.5 ± 27.9)	0.11

Values are either n (%) with P-value by Fisher's exact test or mean ± SD with P-value by Student's t-test.

Discussion

To our knowledge, this is the first study to test the efficacy of homoeopathy in cardiac surgery. It allowed a quantitative monitoring of several clinical and biological parameters but failed to show that the homoeopathic combination of *A. montana* and *B. alba* was better than a placebo in reducing blood loss, systemic inflammation and myocardial ischaemia after aortic valve surgery.

The study was calibrated to detect a 25% decrease in blood loss. That choice was guided by clinical considerations. The difference observed was a decrease of about

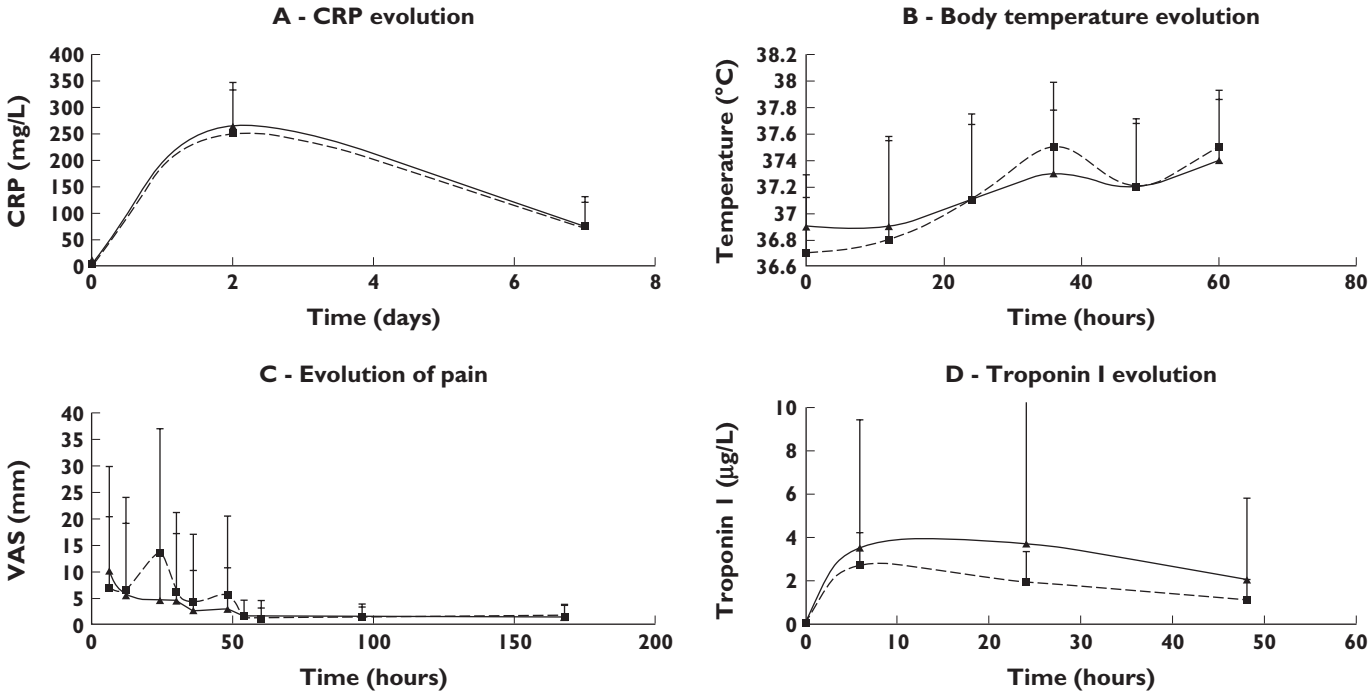

Figure 2

Evolution of secondary end-points in each group: C-reactive protein (a), body temperature (b), pain (c), troponin Ic (d). Homeopathy (–▲–); Placebo (–■–)

20% (156.2 ml), but the study was not sufficiently powered for such a difference; in other words, the reduction of blood loss was about 20% in favour of the tested treatment but the statistical power of detecting such a difference was only 28%. The fact that there was a higher variability in one group made the usual calculation of power using normality rather unsatisfactory. Thus, a nonparametric approach, namely a bootstrap method, was used to find the precision of the estimate through the 95% CI of the difference of the means: the 2.5th and 97.5th percentiles of the distribution were –48 and 445, respectively.

Aortic valve surgery was chosen because this procedure is well standardized and because it allows precise blood-loss measurement. Besides, it was supposed to be an adequate model to test the anti-inflammatory properties of the treatment; however, the results did not support the hypothesis that homoeopathic granules of *A. montana* and *B. alba* have anti-inflammatory properties, although previous *in vitro* and *in vivo* animal studies have shown that *Arnica* preparations have anti-inflammatory, analgesic, antimicrobial, positive inotropic, and hepatoprotective properties [18, 19]. The present results are, however, consistent with a previous meta-analysis and with several additional randomized placebo-controlled trials showing no benefit of *A. montana* in reducing inflammation [2–8].

In 1998, Ernst and Pittler reviewed eight placebo-controlled clinical trials published between 1976 and 1991 that evaluated the efficacy of *A. montana* in the treatment of muscle soreness, pain, postsurgical bleeding and bruising, and 3-month poststroke mortality. They concluded that most of those trials had design flaws and did not provide evidence of benefit beyond that of placebo [2].

Other double-blind randomized trials were published between 1997 and 2007. Hart *et al*. investigated the effect of oral *Arnica* C 30 for the treatment of pain and infection after hysterectomy in 93 women and found no statistically significant differences concerning the rates of infection and postoperative pain ($P > 0.3$) [3]. Ramelet *et al*. evaluated sublingual *Arnica* 5 CH in 130 patients undergoing saphenous vein stripping and found no significant difference regarding postoperative haematoma [4]. Stevinson *et al*. evaluated the efficacy of two concentrations of oral *Arnica* (30 CH and 6 CH) in 64 patients undergoing elective carpal tunnel surgery and could not reveal a benefit of *Arnica* over placebo regarding the severity of pain and of bruising [5]. Seeley *et al*. evaluated oral *Arnica* in 29 patients undergoing elective rhytidectomy during facelifts and found no significant differences in subjective patient or professional assessments of bruising and colour changes. However, an objective assessment showed a smaller area of ecchymosis in the *Arnica*-treated group on postoperative days 1 and 7 [6]. Paris and colleagues evaluated a complex of homoeopathy: *A. montana* 5 CH, *B. alba* 5 CH, *Hypericum perforatum* 5 CH and *Ruta graveolens* 3 DH on cumulated morphine use after knee ligament reconstruction and found that the complex was not superior to placebo [7]. Overall, the efficacy of homoeopathic treatments in surgical contexts is still controversial. In obstet-

rics, evaluating the effect of *A. montana* and *Bellis perennis* on blood loss, Oberbaum *et al*. found that the mean haemoglobin levels remained the same after homoeopathic treatment whereas they decreased significantly in the placebo group (12.7 *vs.* 11.6; $P < 0.05$); they concluded that the homoeopathic association may reduce postpartum blood loss [9].

The present study tested a single combination, identical for all patients, with no adaptation of the treatment to each patient, whereas prescriptions of homoeopathic treatments are usually and essentially patient-specific. The choice of a single treatment was made because of the 'Proof of Concept' nature of the study: we tested more the anti-inflammatory effect than the clinical efficacy. Therefore, our conclusion is limited to the tested drugs within the context of cardiac surgery and should not be extended to the most frequent use of *Arnica* granules, i.e. mild trauma, especially in children.

Conclusion

This study suggests that there is no effect of *A. montana* 5 CH and *B. alba* 9 CH in reducing postoperative haemorrhage, transfusion, pain, inflammation or myocardial injury after aortic valve replacement with CPB.

Competing interests

The present study was financially supported by Laboratoires Boiron, Sainte-Foy-lès-Lyon, France and was conducted in total independence by the Centre for Clinical Investigation, Lyon, France. The sponsor helped in designing the study but was involved neither in data collection, analysis, or interpretation nor in drafting the manuscript. The decision to submit for publication was part of the study protocol.

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